Long term results of radiofrequency ablation (RFA) for irresectable colorectal liver metastases: a potentially curative intervention

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Abstract

The long-term results and prognostic factors of radiofrequency ablation (RFA) for irresectable colorectal liver metastases (CRLM) in a single centre with >10-years of experience were retrospectively analyzed. One-hundred patients with irresectable CRLM (sizes 0.2–8.3cm; mean 2.4cm) underwent a total of 126 RFA sessions (237 lesions). Mean follow-up time was 29.0 months (range 6-93 months). Lesion characteristics (size, number and location), procedure characteristics (percutaneous or intraoperative approach), major and minor complications were carefully noted. Local-control, mean-survival-time, recurrence-free and overall survival were statistically analyzed. No direct procedure-related deaths were observed. Major complications were present in 8 patients. Local RFA-site recurrence was 12.7% (n=30/237) (for tumour-diameters <3cm, 3-5cm and >5cm this was respectively 5.6%(n=8/143), 19.5%(n=15/77) and 41.2%(n=7/17)). Centrally located lesions recurred more often than peripheral ones (21.4%(n=21/98)) versus 6.5%(n=9/139); p=0.009). Including additional treatments for recurring lesions when feasible, lesion-based local control reached 93%. Mean survival-time from RFA was 56 (95%CI 45-67) months. Overall 1, 3, 5 and 8 year-survival from RFA was 93%, 77%, 36% and 24%. RFA for irresectable CRLM is a safe, effective and potentially curative treatment option, with long term results comparable to prior investigations concerning surgical resection. Factors determining success are lesion-size, number of lesions and location.
Introduction

Colorectal carcinoma is one of the most common malignancies in Western countries. In 20-25% of patients with colorectal carcinoma (synchronous) liver metastases are present at the time of diagnosis of the primary tumour. Another 20-30% of patients develop (metachronous) liver metastases and these usually arise within 3 years after initial treatment of the primary tumour. In Europe and the United States, colorectal liver metastases (CRLM) are the most frequent cause of malignant hepatic tumours. The prognosis of patients with untreated CRLM (receiving only symptomatic therapy) is poor with a median survival rate of 4.5 to 12 months, depending on the extent of metastatic disease at the time of diagnosis. Chemotherapeutics, using oxaliplatin and fluorouracil (5FU), can provide prolongation of survival in a palliative setting with median survival of approximately 18 months. More recent results show a median survival of 21.7 months for patients treated with capecitabine, irinotecan and oxaliplatin. Surgical resection is still considered the only method for definite treatment of malignant liver tumours by many. Resection of liver metastases with curative intent results in a 5-year overall survival rate of 24-58% and a 10-year survival rate of 28%. It is not uncommon, particularly in patients with primary colorectal carcinoma, for the liver to be the only site of metastatic disease. Unfortunately, approximately 70 to 80% of patients with metastases confined to the liver are not suitable candidates for resection due to either tumour anatomy (number, size and/or locations), extended extrahepatic disease and/or impaired general health status. Therefore, several other local treatment methods such as tumour ablation, originally considered palliative procedures, have been investigated. Radiofrequency ablation (RFA) has shown promising results in the recent literature. It is a procedure with a relatively low complication rate (less than 10%, mostly minor complications, often unnecessary to treat) and a very small risk of death (<1%), notably when compared to resection. The aim of this study is to retrospectively describe the long term results and predictive factors of RFA for irresectable CRLM.

Materials and methods

Patient selection, demographics and follow-up
One-hundred (59 male; 41 female) patients with CRLM that were treated with RFA alone or in combination with resection between January 1999 and June 2009 during a total of 126 sessions (237 lesions) were retrospectively included. Mean age at the time of RFA was 63 years (range 35-83). Patients with a follow-up period less than 6 months after the RFA procedure were excluded. To retrospectively assess the pre-
procedural lesion characteristics (size, number and location of the lesions), procedural characteristics (open or percutaneous approach) and to document all major and minor complications, treatment responses and recurrences elsewhere, the medical history (including the pre-procedural and follow-up scans and the intra-operative ultrasound report) of all patients was carefully evaluated using our electronic database (dismissal, referral and other medical letters, operation and radiology reports). Every new oncological event (local recurrence, new metastases (intra- or extrahepatic) and death) was recorded into the database. Missing data were obtained by contacting general physicians. Major complications were defined as complications that, if untreated, might threaten the patient’s life, lead to substantial morbidity and disability, result in hospital admission or substantially lengthen hospital stay, as described by the International Working Group of Image-guided Tumour Ablation. Minor complications included typical post-ablation syndrome symptoms (fever, pain, nausea and vomiting) if present >4 days after the RfA procedure. Complications were further divided into two causal categories: those secondary to RF electrode placement (pneumothorax, infection and bleeding) and those secondary to thermal injury (damage to adjacent organs and grounding pad burns). Lesion location was classified as either central or peripheral. Central lesions included lesions in direct contact with or abutting a large vessel measuring at least 4mm.

All patients were considered suitable for either resection, intraoperative ultrasound (IOUS) guided RfA or percutaneous US and/or CT guided Rf A according to a multidisciplinary team including medical oncologists, nuclear physicians, surgical oncologists and both abdominal and interventional radiologists. Patients with a number of maximum 5 CRLM, solitary irresectable lesions ≤7cm or 2-5 lesions <5cm were generally considered suitable for local ablation of the liver disease. Nevertheless, in some cases the inclusion criteria to perform RfA were broadened during surgery: for example if hepatic disease appeared more extensive based on surgical exploration and IOUS (with the patient under general anaesthesia and the sub-costal incision already performed) ablation was performed for lesions up to 8.5cm and a maximum number of 8 lesions in selected cases. In general, a percutaneous approach was preferred for hepatic tumour recurrences, for a limited amount of smaller and superficially located lesions and if a high age or significant co-morbidities were present. The relatively low number of percutaneous approaches is caused by the fact that we started performing these procedures late 2005. Pre-procedural imaging included at least a contrast enhanced CT or MRI scan performed maximum 6 weeks before the procedure and an F18-FDG-PET performed maximum two months before the procedure. Lesions were considered to represent CRLM based upon either pre-procedural PET avidity and/or typical CT and IOUS characteristics. For atypical lesions histology was obtained. For open procedures the definite decision to perform
RFA was based on surgical exploration and IOUS. The follow-up imaging protocol consisted of 3, 6, 9, 12, 18, and 24 month follow-up CT scans and 6, 12, and 24 month follow-up F18-FDG-PET scans followed by annual PET and CT scans, if no recurrence was present (Fig. 1). The procedures carried out on humans were in accordance with the ethical standards of the world medical association (Declaration of Helsinki). For this retrospective study with anonymized subjects approval from the institutional ethical committee was waived.

**Primary tumour treatment**
In patients with liver metastases from colonic carcinoma the primary tumour was resected before treatment of the liver metastases. Patients with rectal carcinomas received neo-adjuvant radiotherapy of the rectal cancer, followed by treatment of the liver disease and subsequently resection of the primary tumour.

**Pre- or postprocedural chemotherapy**
Patients with synchronous CRLM suitable for resection and/or RFA received adjuvant chemotherapy schemes (regimens have changed several times during the last decade) after the procedure. Patients with metachronous CRLM were not uniformly treated with adjuvant chemotherapy. Adjuvant chemotherapy with 5-FU and leucovorin, combined with irinotecan and/or oxaliplatin, is currently the standard treatment following RFA for CRLM. Patients with initially advanced liver disease received palliative chemotherapy. If partial response was present and the liver disease was downstaged enough to enable resection and/or ablation with curative intent, patients were considered suitable for either intraoperative treatment (resection and/or ablation) or percutaneous RFA.

**Extrahepatic disease**
Limited extrahepatic metastatic disease was not considered a contra-indication if all metastases could still be resected, ablated or irradiated with curative intent.

**Intra-operative RFA**
All patients were admitted to our centre at least one day before surgery. A subcostal incision laparotomy was performed for optimal liver exposure. The abdominal cavity was explored in order to exclude extra-hepatic tumour manifestations. IOUS (Prosound Alpha10; 10.0 MHz linear intraoperative probe and 5.0/1.25 MHz convex probe, Aloka, Tokyo, Japan) was performed by an interventional radiologist, who carefully noted the exact size (maximum diameter), number and location of all CRLM. Based upon the size of the lesion and on the proximity of adjacent vital structures 2.0 – 5.0cm expandable-needle electrodes (LeVeen, Boston Scientific, USA) were
manually placed using ultrasound guidance by interventional radiologists in close collaboration with surgical oncologists to avoid damage to surrounding organs and structures. Since 2008 we have been using a novel bipolar RfA unit for lesions larger than 3.5cm (InCircle, RFMedical, Fremont, USA) in eight selected patients. All electrodes were connected to a commercially available RF generator (RF3000, Boston Scientific, USA). Ablations were performed according to the protocols provided by the manufacturers. Primary endpoints for a technically successful ablation were at least two increases in tissue impedance (roll-off) with an interablation delay of 30 seconds and a fully hyperechoic ablation zone including a tumour-free margin of at least one centimetre on IOUS. If necessary the needle electrodes were repositioned for one or more overlapping ablations. Since early 2007 we started using contrast-enhanced intraoperative ultrasound (CE-IOUS) in selected cases (especially large or centrally located lesions) as secondary endpoint, several minutes after ablation to detect residual vital tumour tissue. If deemed necessary, due to the proximity of a large portal vein or hepatic artery, a so called Pringle manoeuvre was performed, placing a large haemostat to temporarily interrupt the flow of blood through both the hepatic artery and the portal vein. Needle track ablation was performed to avoid needle track haemorrhage and possible seeding of tumour cells.

**Percutaneous CT and/or US guided RFA**

All procedures were performed under general anaesthesia. Patients were positioned either in a supine or prone position based upon the optimal percutaneous approach of the tumour. The procedure was planned on at least an unenhanced CT just before the procedure. If the lesions were invisible on these unenhanced images either a contrast enhanced CT scan and/or ultrasound guidance was chosen for image guidance. The RfA needles were carefully positioned using CT fluoroscopy aiming at a tumour free ablation zone of at least 1cm. Again needle track ablation was performed to avoid needle track haemorrhage and possible seeding of tumour cells. For tumours with a priori high probability on needle track haemorrhage (centrally located tumours or impaired haemostasis) we used co-axial needle systems (CoAccess, LeVeen, Boston Scientific, USA) and manually placed a number of small haemostatic foam plugs (Willospon, WillPharma, Netherlands) in the needle track while retracting the co-axial needle. Primary endpoints for a technically successful ablation were at least two increases in tissue impedance (roll-off) with an interablation delay of 30 seconds. For lesions larger than 3cm a contrast enhanced CT scan directly after the procedure was used as secondary endpoint. The ablation zone was defined as the non-enhancing hypodense region 70 seconds after start of contrast injection. When considered necessary, additional overlapping ablations were performed after electrode repositioning.
Statistical analysis
Local control, mean survival-time and 1-, 3-, 5- and 8-year overall survival were statistically analyzed. Kaplan–Meier plots of survival were acquired using standard statistical analysis software SPSS (SPSS for windows version 11.5, Chicago, USA). Factors determining local success, progression free and overall survival were compared using log rank analysis and p<0.05 was considered significant. Variates investigated were: number, position and size of CRLM, percutaneous versus intraoperative approach, operator experience, the presence of extrahepatic disease and a history of liver resection and/or pre- or postprocedural chemotherapy.

Results

Patient and lesion characteristics (Table 1 and 2)
One-hundred patients with 237 irresectable histologically proven CRLM underwent a total of 126 RFA sessions. Mean number of treated CRLM in a single session was 1.9 (range 1-8). Mean size of ablated CRLM was 2.4cm (range 0.2-8.3cm). Mean follow-up time was 29 months (range 6-93 months).
Table 1: Patient characteristics: age, gender, primary tumour, time of CRLM diagnosis, chemotherapy, additional surgical resections and the presence of limited extrahepatic disease.

<table>
<thead>
<tr>
<th>Patients</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (range)</td>
<td>63 (35-83)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 59, Female 41</td>
</tr>
<tr>
<td>Primary tumour</td>
<td>Colon 71, Rectum 29</td>
</tr>
<tr>
<td>Diagnosis metastasis</td>
<td>Synchronous 34, Metachronous 66</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>None 49, Pre-RFA 43, Post-RFA 5, Pre- and post-RFA 3</td>
</tr>
<tr>
<td>Surgical resections*</td>
<td>Pre-RFA 8, In same session with RFA 37, Post-RFA 8</td>
</tr>
<tr>
<td>Extrahepatic disease**</td>
<td>Lung metastases 4, Lymphadenopathy 2, Intraperitoneal deposition 1</td>
</tr>
</tbody>
</table>

* Of other colorectal liver metastases

** Limited extrahepatic disease diagnosed at same time as or prior to detection of liver disease

Table 2: Lesion characteristics: number, size and location of lesions.

<table>
<thead>
<tr>
<th>Number of lesions</th>
<th>237</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of lesions (in cm)</td>
<td>average size (min-max) 2.4 (0.2-8.3)</td>
</tr>
<tr>
<td>Location</td>
<td>Central 98, Peripheral 139</td>
</tr>
</tbody>
</table>

Procedure characteristics (Table 3)

Of the 237 RFA procedures 221 were performed during open laparotomy and 16 were approached percutaneously. An intraoperative Pringle manoeuvre was performed during RFA in 5 patients. RFA was considered technically successful in all cases.
Table 3: Procedure characteristics: approach, device and operator experience.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Intraoperatively US-guided</th>
<th>221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrode</td>
<td>Percutaneously CT-guided</td>
<td>16</td>
</tr>
<tr>
<td>Monopolar 2.0cm</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Monopolar 3.0cm</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Monopolar 3.5cm</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Monopolar 4.0cm</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Monopolar 5.0cm</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Bipolar 4.0cm</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Bipolar 5.0cm</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Operator experience</td>
<td>History ≤10 procedures</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>History &gt;10 procedures</td>
<td>175</td>
</tr>
</tbody>
</table>

Complications (Table 4)
There were no direct procedure-related mortalities. One 80-year-old male patient with a history of coronary artery disease died three days after RfA due to an autopsy proven massive myocardial infarction. Obduction revealed a fully ablated CRLM. Major complications were present in 8 patients, minor complications in 18 patients.

Table 4: Mortality, major and minor complications.*

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Directly related to RFA</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect</td>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Major complications</td>
<td>Related to electrode placement</td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Related to thermotherapy</td>
<td>Grounding pads burning wounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diaphragm perforation with pleural empyema requiring drain</td>
</tr>
<tr>
<td>Minor complications</td>
<td>Post-ablation Σ symptoms &gt;4 days</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>Other</td>
<td>Benign cardiac arrhythmia</td>
<td>1</td>
</tr>
</tbody>
</table>

* Classified according to the International Working Group of Image-guided Tumour Ablation.21

Recurrence (Fig. 2, 3)
After a median follow-up of 29 months (6-93) in total sixty-eight patients (68%) had a recurrence either at the RfA-site or elsewhere. Including additional treatments (re-RfA, surgical resections and/or radiotherapy) for recurring lesions when feasible 54% (54/100) of all patients where disease-free after a follow-up period of at least 6 months.
Fig. 2: Flowchart showing the outcome of all patients after RFA. The final outcome after additional local treatments (RFA or other local treatments with curative intent) for recurrence is displayed in red (asterisk).

The first oncological tumour-recurring event consisted of thirty patients with local recurrence at the RFA site: 9 isolated at the RFA-site, 8 at the RFA-site in combination with limited (locally treatable) disease elsewhere and 13 at the RFA-site in combination with extended disease elsewhere. In 7 patients a limited number of new liver metastases were treated with either resection and/or RFA. In 6 patients limited recurrence (re-treatment possible) was found outside the liver (lung 4, lymph node 1 and adrenal gland 1). In 38 patients recurrence was judged as extended disease, unsuitable for local treatment. The percentage of patients with recurring disease not at the RFA-site was 50.0% (28/56) for initially solitary CRLM and 70.5% (31/44) for initially multiple CRLM (>1) (p=0.04).
Local RFA-site recurrence was 12.7% (n=30/237) (for tumour-diameters <3cm, 3-5cm and >5cm this was respectively 5.6% (n=8/143), 19.5% (n=15/77) and 41.2% (n=7/17)). Centrally located lesions recurred more often than peripheral ones (21.4% (n=21/98) versus 6.5% (n=9/139); p=0.009). Including additional treatments for recurring lesions when feasible, lesion-based local control (percentage of locally controlled lesions) reached 93%.

Fig. 3: Recurrence free survival plots for different numbers of CRLM treated (A), for different sizes of the largest CRLM present in every patient (B), for patients who also had surgical resections for other CRLM before or within the same session as the RFA procedure versus “RFA alone” patients (C) and for patients with versus without (neo)adjuvant chemotherapy regimens, excluding patients who only received chemotherapy for tumour recurrence at a later time-point.
Overall survival (Fig. 4)

Mean survival-time from RFA was 56 (95%CI 45-67) months. Overall 1, 3, 5 and 8 year-survival from RFA was 93%, 77%, 36% and 24%. Outcome was dependant on maximum size of the largest CRLM and on the number of lesions (Fig. 4A,B). No significant difference could be made between the percutaneous and intraoperative approach, because of insufficient numbers for any comparison to be made.

Fig. 4: Kaplan-meier survival plots for different numbers of CRLM treated (A), for different sizes of the largest CRLM present in every patient (B), for patients who also had surgical resections for other CRLM before or within the same session as the RFA procedure versus “RFA alone” patients (C) and for patients with versus without (neo)adjuvant chemotherapy regimens, excluding patients who only received chemotherapy for tumour recurrence at a later time-point.
Discussion

In patients with liver metastases unsuitable for resection, an alternative treatment method such as RFA may be helpful in achieving local tumour control and even curation. However, drawing general conclusions about the impact of RFA on survival is difficult. Patients referred to our institution represent a selected population. Also, our group of patients is very heterogeneous with regard to tumour characteristics and treatment regimes. The different treatment strategies (preoperative chemotherapy, previous resection and/or RFA, portal vein ligation during RFA procedure, resection following RFA, postoperative chemotherapy) possibly obscure the effect of RFA. Nevertheless, in our series a five year overall survival of 36% remains promising, especially since we included all patients in whom we performed RFA (tumours up to 8.3cm in diameter, a maximum number of 8 lesions treated in one session and chemotherapeutically downstaged patients with initially advanced disease). Due to the lack of randomized trials comparing RFA with another treatment modality (such as chemotherapy or surgical resection), the precise impact of RFA on survival is still ill defined. In general patients treated with RFA, having irresectable liver metastases, could be considered as having more, larger and/or bilobar liver metastases than patients amenable for surgical resection. Therefore, it should be emphasized that patients treated with RFA have a poorer prognosis than patients treated with resection of their metastases. Recent literature and our study provide intriguing information regarding the results of RFA. The limited available information on long-term outcomes suggest that RFA has a positive impact on overall survival. Reported overall median survival after RFA varies from 28.9 to 45.5 months. This rate is even better for patients with fewer (<5) or smaller (<5cm) tumours. Some are even arguing comparable outcome after resection and RFA of low-volume liver disease. Although many still consider RFA to represent a palliative treatment option, in our institute the treatment is always performed with curative intent (only if the entire macroscopically visible tumour load can be ablated with or without additional resections). Our results and the results from other long-term follow-up studies show that full curation can be achieved in a reasonable percentage of patients. The inclusion criteria for performing RFA are continuously broadening: larger lesions, more difficultly localized lesions, a larger number of lesions and shifting definitions of how limited extrahepatic disease is defined. Therefore, the overall results are mainly determined by the treatment limits that we set ourselves and should always be interpreted in the context of rigorous patient selection. Resection is the gold standard of management, but this still only applies to the minority of patients with liver metastases. As previously mentioned the 5-year overall survival rate after surgical resection of colorectal metastases is 24-58%. The prognosis of patients following resection of solitary liver metastases is
even better, with a recent report describing a survival rate exceeding 70%. Although in recent years more and more patients are considered amenable for surgical resection, clear definitions on resectability are lacking.22

Ever since the widespread introduction and application of RFA as a local treatment method of liver metastases, the issue of recurrence has been of great importance. Distant recurrence (elsewhere in the liver or extrahepatic) rates vary from 28 to 84%.17,20 Reported local recurrence rate (at the RFA site) ranges widely, from 2 to 60%.19,28,31-33 In our series 12% had local RFA site recurrence. Since local recurrence often represents a small marginal focal spot, many recurrences can be re-treated with RFA relatively easily. Definite local control after additional ablations (93% in our study) may therefore be a more important parameter. Furthermore, since several patients with local RFA site recurrence also have advanced recurrences elsewhere (which made him/her unsuitable for re-ablation) the real percentage of lesions that could theoretically be locally controlled after secondary sessions is probably still underestimated. Factors predicting local RFA site recurrence were tumour size and centrally located lesions. The latter is probably caused by both the so called heat sink effect (continuous cooling of tumour tissue by adjacent vessels), but maybe also due to the use of less oversized needle electrodes, to prevent damage to the main bile ducts. Our group has previously described moderately promising results for RFA of larger liver tumours using a novel bipolar unit.35 Furthermore, there is increasing evidence that trans-arterial chemoembolization (TACE) with irinotecan drug-eluting beads before or within 24 hours after RFA can increase ablation sizes and improve local control in selected patients.36,37

To conclude, RFA for irresectable CRLM is a safe and effective treatment option, which can provide long-term survival-benefit comparable to surgical resection. Factors determining local success are lesion-size, number of lesions and location. The technique can be considered at least a valuable asset to surgical resection. To define the true place of RFA within the different treatment modalities for CRLM, further studies are needed. Such studies will probably be complicated by the evolving definitions of resectability, consequent expanding indications for hepatic resection of CRLM38-40 and the use of modern, more effective cytotoxic agents, such as oxaliplatin and irinotecan.41 The management of colorectal liver metastases requires a multimodality treatment approach. The prognosis of solitary and multiple liver metastases is improving and the search for the optimal treatment strategy for the individual patient is challenging. Thus, proper patient selection and multidisciplinary management of CRLM is crucial. Recurrence remains an ongoing concern in evaluating the management of patients with (colorectal) liver metastases. Overall, the results of our study are encouraging and suggest not only prolongation of survival but also a
considerable chance at achieving full curation in selected patients. Advantages of RFA include the relative safety, simplicity and the possibility to repeat the procedure. It is important to emphasize that the prognosis of CRLM is not as ominous as previously thought.
References


Long term results of radiofrequency ablation (RFA) for irresectable colorectal